II. REMARKS

A. Status of the Claims

This is in Response to the Final Office Action dated July 9, 2008. A petition for three-month extension of time and corresponding fee accompanies this Amendment.

Claims 1-8 and 10-22 were previously canceled without prejudice.

Claims 9 and 23-29 are pending.

Applicants acknowledge that all objections and rejections recited in the November 21, 2007 Office Action have been withdrawn. Thus Applicants address the new rejections under 35 U.S.C. 103(a) as recited in the Final Office Action of July 9, 2008 in the present Response.

Applicants respectfully request reconsideration of this application based on this Response to Final Office Action.

B. Claim Rejections- 35 U.S.C. § 103

In the Office Action mailed on July 9, 2008, claims 9 and 23 to 29 were rejected under 35 U.S.C. 103(a) as being obvious over Lage et al. (Virchows Arch 2001 438:567-573), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53).

In the Office Action, the Examiner asserts that: "Lage et al. teach the production of a monoclonal antibody to GPC3 using an oligopeptide of amino acids 537-556 of GPC3" and "teach that the glycosyl-phosphatidylinositol protein anchor GPC3 is expressed in hepatocellular carcinomas, decreasing in expression in tumor grade." See Office Action, page 3, second full paragraph.

In the Office Action, the Examiner also asserts that: "Steplewski et al. teach that mouse monoclonal antibodies are humanized to overcome the problem of short half-life and immunogenicity of murine monoclonal antibodies in humans", and that humanized mouse monoclonal antibodies generated using Cγ1 , Cγ2, Cγ3 and Cγ4 human heavy chains and human CK light chains "can mediate antibody dependent cell mediated cytotoxicity, ADCC, in vitro in the presence of peripheral blood monocytes." See Office Action, page 3, fourth full paragraph to page 4, lines 1 to 2.

In the Office Action, the Examiner also asserts that: "Dillman teaches that IgG1, IgG2, IgG3 and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity. See Office Action, page 4, first full paragraph.

In the Office Action, the Examiner also asserts that: "Mast et al teach that GPC3 is expressed on the surface of HepG2 cells" and that "Midorikawa et al teach that GPC3 protein is found in elevated levels in HepG2 cells and 22 of 52 hepatocellular carcinomas examined." See Office Action, page 4, second and third full paragraphs.

In view of the aforementioned assertions, the Examiner concluded that it would be prime facie obvious to one of skill in the art to achieve the present invention from the disclosure of the above-referenced citations.

Applicants respectfully submit that Lage, at page 570, right-column, lines 9-15 and Fig. 1, discloses that Western-blot analysis of a stomach cancer cell line EPG85-257RNOV using the disclosed antibody Be-F4 revealed the analogous results as the Northern blot analysis of stomach cancer (See Lage, page 570, right-column, line 13-15). On the other hand, Lage discloses the Western-blot analysis and histological staining of hepatocarcinoma (See Lage, page 571, left-column and right-column text and Figs. 2 and 4) and concludes that "HCC cells constantly showed a decreased staining intensity when compared with the staining signal obtained in noncancerous liver cells from the same section (See Lage, page 571, right column, line 1-4)" and "[i]n contrast to the non-neoplastic hepatocytes, the cellular p62 content was unambiguously reduced in all malignant cells." (See Lage, Abstract line 11-13).

Therefore, it is evident from the disclosure of Lage that GPC3 is not highly expressed in

a protein level in hepatocarcinoma cells. Applicants respectfully submit that the disclosure of Lage is inconsistent with the disclosure of Midorikawa wherein GPC3 is highly expressed in HepG2 cells and hepatocarcinoma cells, and with the disclosure of Mast that GPC3 is expressed on the surface of HepG2 cells (Applicants note that Mast does not mention the level of expression). Therefore, Applicants respectfully submit that one of skill in the art would not look to combine the teachings of Lage, Midorikawa and Mast because they are inconsistent with each other.

Even if Lage discloses a GPC3 monoclonal antibody obtained using an oligopeptide of amino acids 537-556 of GPC3, one of skill in the art would not combine Lage with Midorikawa and Mast which provide opposite teachings from Lage. Thus, one of skill in the art would not look to combine these references, thus the present invention is not obvious from the inventions disclosed in these references.

For the foregoing reasons, withdrawal of the rejection of claims 9 and 23 to 29 under 35 U.S.C. 103(a) is respectfully requested.

In the Office Action mailed on July 9, 2008, claims 9 and 23 to 29 were rejected under 35 U.S.C. 103(a) as being obvious over Filmus et al. (US Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85:4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327:577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53).

In the Office Action, the Examiner asserts, *inter alia*, that: "Filmus et al teach the production of a monoclonal antibody to GPC3 using the last 70 amino acids of human GPC3" and that "Filmus et al. teach that the monoclonal antibody 1 G12 bound strongly to human liver tumor cells." See Office Action, page 5, second full paragraph. The Office Action also admits that "Filmus et al does not teach that the antibody has any cytotoxic activity *in vitro* against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells or a humanized form of the antibody." See Office Action, page 6, first full paragraph.

The Examiner repeats his assertions regarding the Steplewski, Dillman, Mast and Midroikawa et al. references as discussed above.

In view of the foregoing assertions, the Examiner concluded that it would be prime facie obvious to one of skill in the art to achieve the present invention from the disclosure of the citations. Applicants respectfully submit that the unconjugated antibodies disclosed in Filmus (1 G12, 8H5) do not have cytotoxic activity against hepatocarcinoma cells such as HepG2 cell line. Moreover, Steplewski fails to disclose that a mouse monoclonal antibody having no cytotoxicity, e.g. 1 G12 antibody, may be humanized to impart cytotoxicity.

Applicants respectfully submit that, the antibody 1 G12, as disclosed in Filmus is also described in International Patent Publication W02007/137170, a copy of which is attached as Appendix A. International Patent Publication W02007/137170 discloses in paragraph [0202] that "The cytotoxic activities of the anti-GPC3 antibodies (1 G12, 8H5) with a secondary antibody conjugate were evaluated on the Glypican-3 positive HepG2 and Hep3B cell lines." See International Patent Publication W02007/137170, paragraph [0202]. Applicants respectfully submit that the unconjugated antibodies (1 G12, 8H5) were not observed to have cytotoxic activity on these cell lines.

In addition, Applicants submit herewith a Data Sheet, attached as Appendix B (also available from the website http://www.biomosaics.com/pdfs/B0134R%20%20data%20sheet%202007. pdf), the antibody 1 G12 is distributed in a commercially available manner, and a person skilled in the art can easily confirm that the antibody 1 G12 does not have cytotoxic activity against hepatocarcinoma cells such as HepG2 cell line.

In the Office Action, the Examiner alleged *inter alia* that it was obvious for a person skilled in the art to humanize the monoclonal antibody 1 G12 which strongly bind to human hepatocarcinoma cells using the humanizing techniques disclosed in Steplewski to create a humanized antibody having cytotoxicity (see page 7, line 4-15 of the Office Action). However, Applicants respectfully submit that although Steplewski teaches that the mouse monoclonal

antibody C017-1A having cytotoxicity may be humanized to overcome the problem of short half-life and immunogenicity, Steplewski fails to disclose that a mouse monoclonal antibody having no cytotoxicity, e.g. 1 G12 antibody, may be humanized to impart cytotoxicity.

The Examiner also alleged that the antibody of Filmus which binds to the amino acids 375-580 of GPC3 was known, and humanized techniques of antibodies as well as humanized antibodies having cytotoxicity were well known in the art, and thus one would prepare a humanized monoclonal antibody against a peptide having the amino acids 375-580 of GPC3 with a reasonable expectation of success (see page 7, line 8-15 of the Office Action). As discussed above, however, since it was well known in the art, or one could easily understand, that the antibody of Filmus, 1 G12 antibody, does not have cytotoxicity, a person skilled in the art could not have been motivated from Steplewski to prepare a humanized antibody having cytotoxicity by humanizing a mouse monoclonal antibody having no cytotoxicity. More likely, a person skilled in the art would recognize it difficult to prepare a humanized anti-GPC3 antibody having cytotoxicity based on Filmus that teaches the monoclonal antibody 1 G12 having no cytotoxicity.

In addition, Filmus discloses that the antibody 1 G12 can detect GPC3 in serum (Example 6). Filmus teaches that GPC3 is released from hepatocarcinoma cells. Mast teaches that GPC3 is expressed on the surface of HepG2 cells and Midorikawa teaches that GPC3 level is elevated in HepG2 cells and 22 out of 52 hepatocellular carcinomas, while Filmus teaches that GPC3 expressed in that way is detected in serum. Accordingly, a person skilled in the art seeking to obtain an antibody having cytotoxicity with the aim of achieving treatment of hepatocarcinoma by damaging hepatocarcinoma cells would not look to combine Filmus with Mast and Midorikawa with a reasonable expectation of success, because Filmus discloses that GPC3 is detected in serum and, as discussed, the antibody 1 G12 cannot exert cytotoxicity against HepG2 cells.

In conclusion, a person skilled in the art could not have conceived of the present invention based on the combination of the cited references.

For the foregoing reasons, withdrawal of the rejection of claims 9 and 23 to 29 under 35 U.S.C. 103(a) is respectfully requested.

Conclusion

Reconsideration of the present application is respectfully requested. If the Examiner has any questions or concerns regarding this response and amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number set forth below.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Sunil Raval
Reg. No. 47,886

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, NY 10018
(212) 736-1940